A Method for Coupling Agent-based Models of Tissue Fibrosis to Logic-based Models of Intracellular Signaling

UNIVERSITY OF VIRGINIA
SCHOOL of ENGINEERING & APPLIED SCIENCE
Department of Biomedical Engineering

S. Michaela Rikard[1], Jia-Jye Lee[1], Thomas L. Athey[4], Shayn M. Peirce[1,2], Jeffrey J. Saucerman[1,2], and Jeffrey W. Holmes[1,2,3]

[1]Department of Biomedical Engineering, [2]Cardiovascular Research Center, and [3]Department of Medicine, University of Virginia, Charlottesville, VA
[4]Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD

INTRODUCTION

- Scar remodeling following myocardial infarction (MI) is a dynamic process involving many cell types, extracellular matrix (ECM), and inflammatory cues.
- Design of post-MI therapies must account for their effects on intracellular signaling, cell-cell communication, and cell-matrix interactions.
- Here we present a new method for coupling a **logic-based differential equation (LDE)** model of **intracellular signaling** in individual fibroblasts with an **agent-based model** (ABM) of **collagen remodeling** by multiple cells in the infarct.
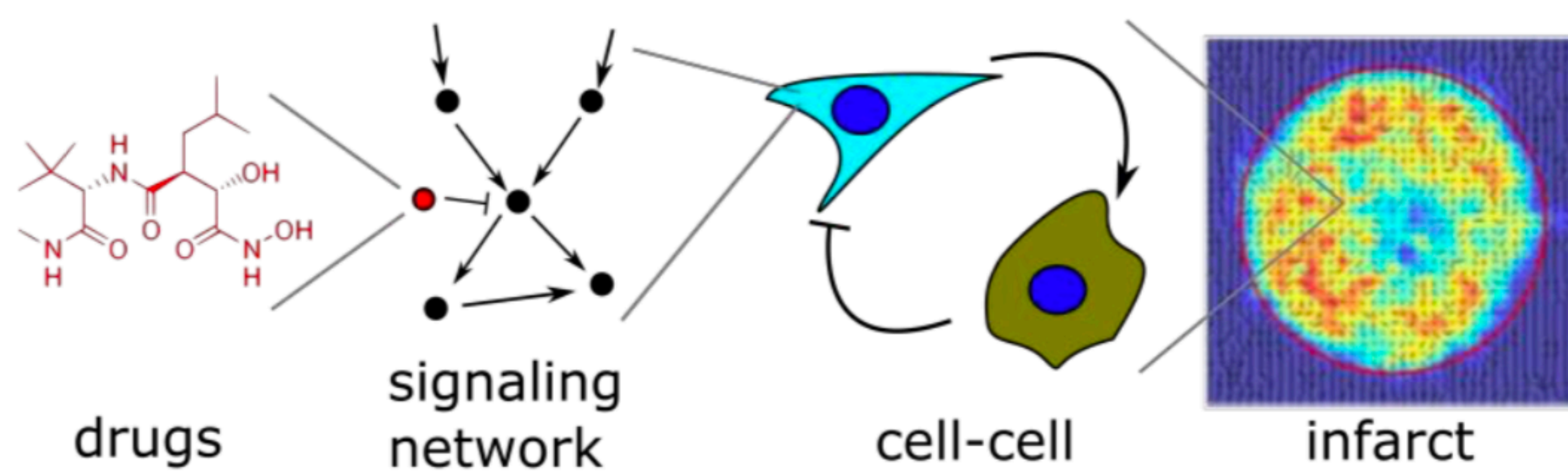

Figure 1. Systems pharmacology model spanning from drug-target interactions to spatial control of cardiac fibrosis.

RESULTS

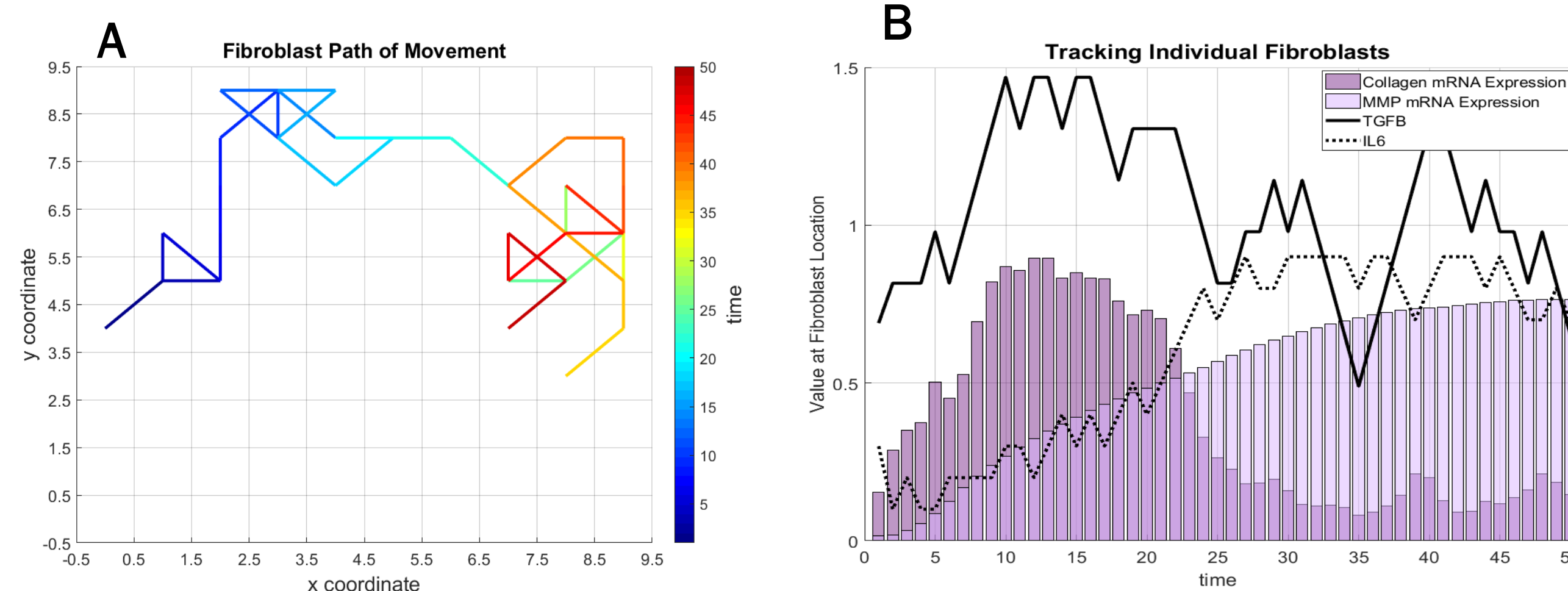### History dependent collagen remodeling

Figure 5. Tracking individual fibroblast histories. **A.** The path of movement for an individual fibroblast in a 10x10 grid space over 50 time steps. **B.** Fibroblast deposition and degradation activity based on environmental TGFβ and Il6 levels.

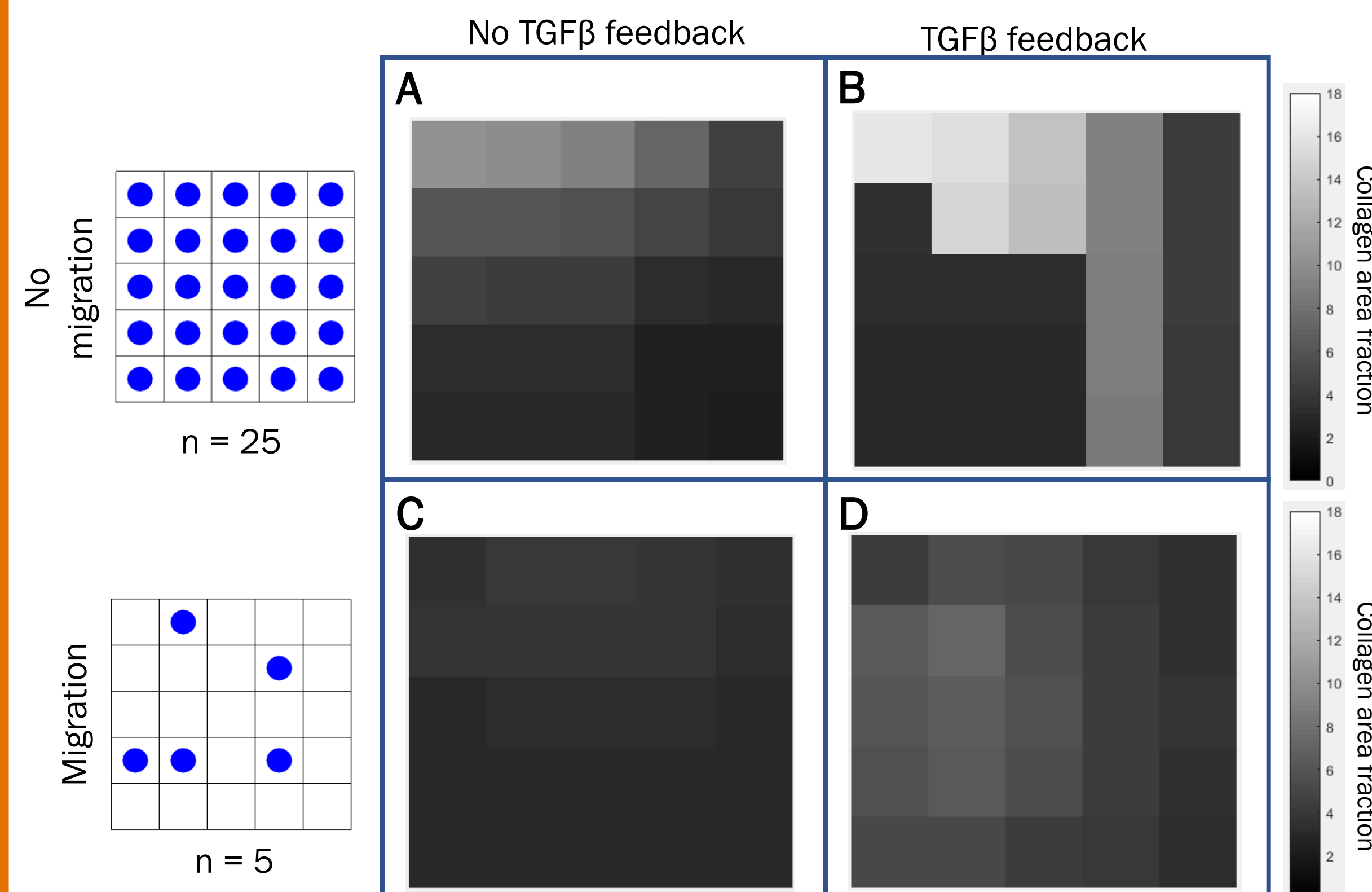### Collagen profile after 7 days

Figure 6. Model predictions of collagen profile after 7 days. Collagen profile without TGFβ feedback (A and C) and with TGFβ feedback (B and D). Results shown for one fibroblast per grid location without cell migration (A and B) and with random cell migration of 5 randomly seeded fibroblasts (C and D).
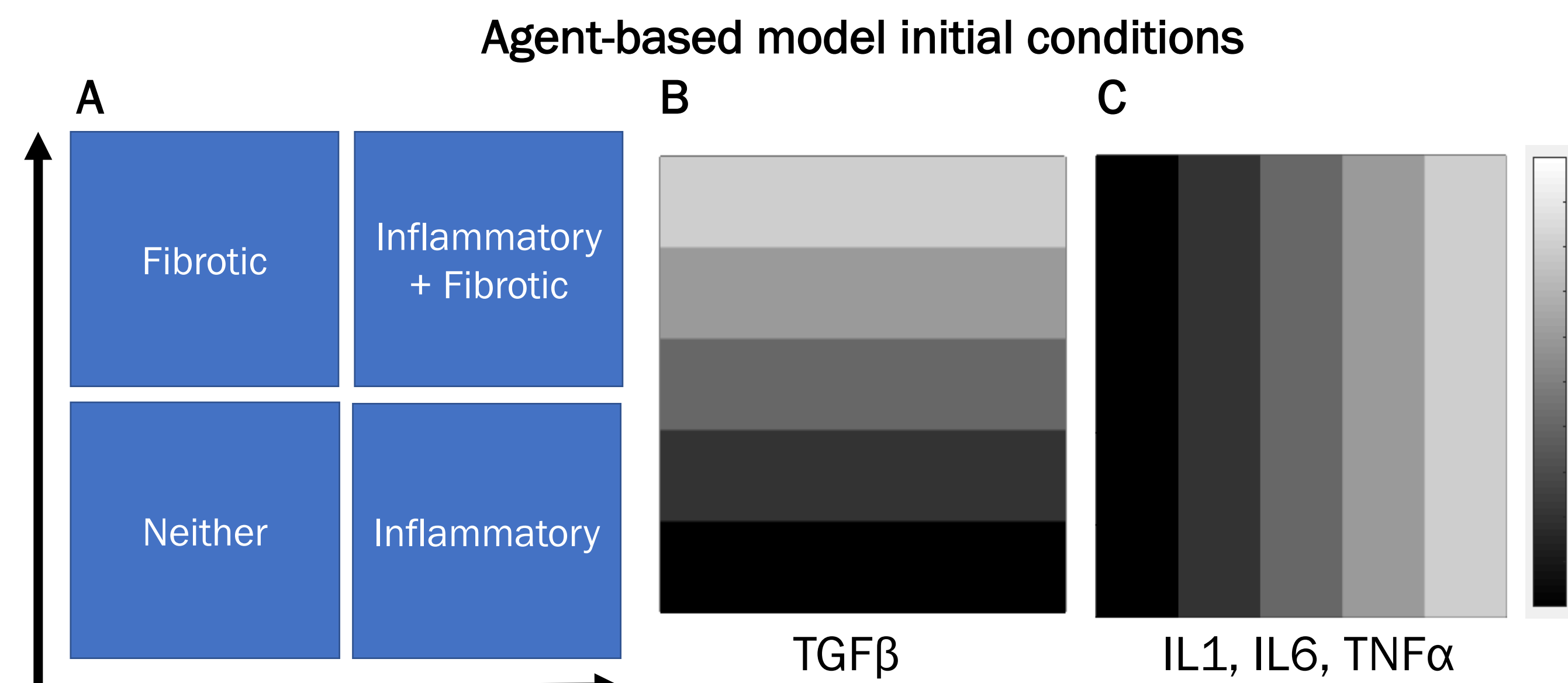
METHODS

Agent-based model initial conditions

Figure 2. Initial conditions for agent-based model. **A.** Chemokine gradients are set up to create different phenotypic regions. **B.** Fibrotic chemokine gradient is initialized from 0 (bottom) to 1 (top). **C.** Inflammatory chemokine gradient is initialized from 0 (left) to 1 (right).
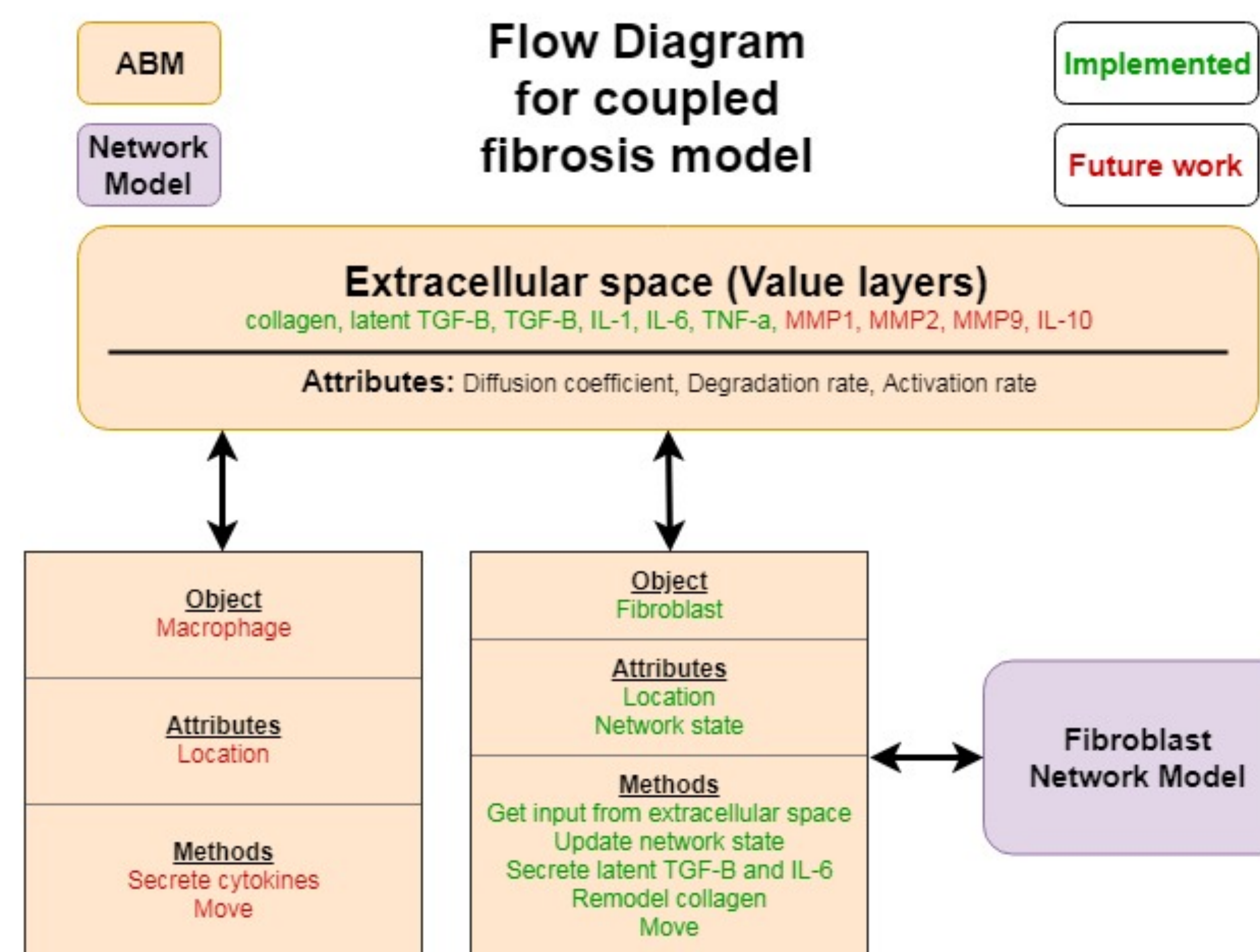
Flow Diagram for coupled fibrosis model

ABM | Network Model | Implemented | Future work

Extracellular space (Value layers)
collagen, latent TGF-B, TGF-B, IL-1, IL-6, TNF-a, MMP1, MMP2, MMP9, IL-10
Attributes: Diffusion coefficient, Degradation rate, Activation rate

Object Macrophage
Attributes Location
Methods Secrete cytokines, Move

Object Fibroblast
Attributes Location, Network state
Methods Get input from extracellular space, Update network state, Secrete latent TGF-B and IL-6, Remodel collagen, Move

Fibroblast Network Model

Figure 3. Flow diagram depicting high level architecture of the coupled model and communication between components of the model.
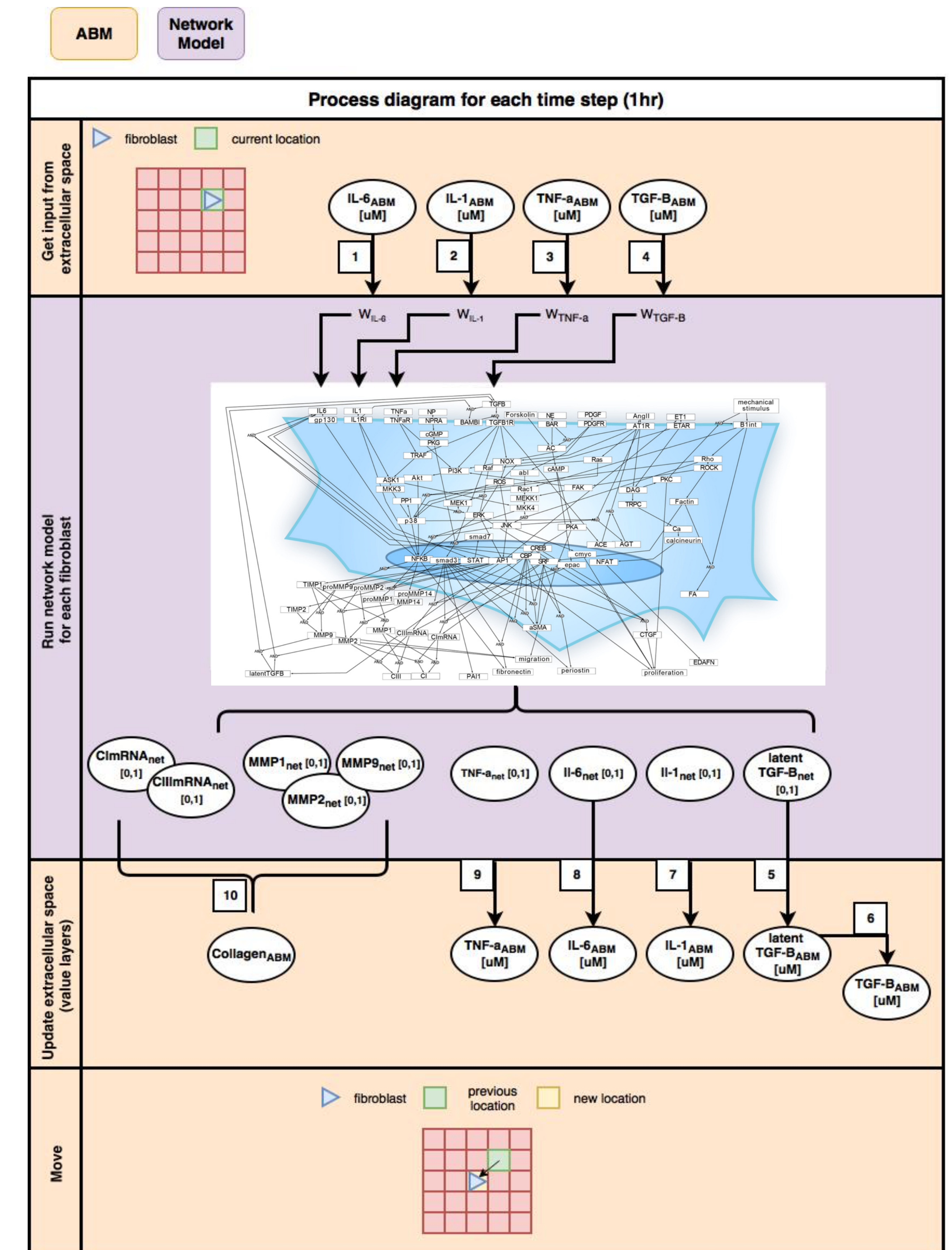

Figure 4. Detailed process diagram depicting the flow of methods for each time step (1 hour). ABM methods are highlighted in orange and network model methods are in purple. Steps involving an equation are numbered, with the explicit equations listed below.

COUPLING EQUATIONS

1. $w_{IL6} = \frac{IL6_{ABM}}{IL6_{sat}}$

2. $w_{IL1} = \frac{IL1_{ABM}}{IL1_{sat}}$

3. $w_{TGF\beta} = \frac{TGF\beta_{ABM}}{TGF\beta_{sat}}$

4. $w_{TNF\alpha} = \frac{TNF\alpha_{ABM}}{TNF\alpha_{sat}}$

5. $\frac{\partial latentTGF\beta_{ABM}}{\partial t} = k_{conv,latentTGF\beta} * latentTGF\beta_{net} - k_{deg,latentTGF\beta} * latentTGF\beta_{ABM} - (k_{gen,MMP2} * MMP2 + k_{gen,MMP9} * MMP9) * latentTGF\beta_{ABM}$

6. $\frac{\partial TGF\beta_{ABM}}{\partial t} = (k_{gen,MMP2} * MMP2 + k_{gen,MMP9} * MMP9) * latentTGF\beta_{ABM} - k_{deg,TGF\beta} * TGF\beta_{ABM}$

7. $\frac{\partial IL1_{ABM}}{\partial t} = k_{gen,IL1} - k_{deg,IL1} * IL1_{ABM}$

8. $\frac{\partial IL6_{ABM}}{\partial t} = k_{gen,IL6} + k_{conv,IL6} * IL6_{net} - k_{deg,IL6} * IL6_{ABM}$

9. $\frac{\partial TNF\alpha_{ABM}}{\partial t} = k_{gen,TNF\alpha} - k_{deg,TNF\alpha} * TNF\alpha_{ABM}$

10. $\frac{\partial Collagen_{ABM}}{\partial t} = k_{gen,Collagen}(CollRNA_{net} + CollIIRNA_{net}) - k_{deg,Collagen}(MMP1_{net} + MMP2_{net} + MMP9_{net}) * Collagen_{ABM}$

Glossary
- IL6 – Interleukin 6
- IL1 – Interleukin 1
- TNFα – Tumor necrosis factor alpha
- TGFβ – Tissue growth factor beta
- MMP1 – Matrix metalloprotease 1
- MMP2 – Matrix metalloprotease 2
- MMP9 – Matrix metalloprotease 9

- k_{gen} – coefficient of generation
- k_{deg} – coefficient of degradation
- k_{conv} – coefficient for conversion from network model output to units of concentration

CONCLUSIONS

- Here we present a novel framework for coupling an ABM and LDE model to study cardiac fibrosis and tissue remodeling post-MI.
- Fibroblasts display **history-dependent collagen remodeling** and migration contributes to **spatial heterogeneity** of the collagen profile.
- This multiscale model will allow for the systematic **testing of pharmacological interventions** which depicts the **drug target** on individual fibroblasts, as well as **tissue level remodeling** in extracellular matrix composition and spatial heterogeneity.